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Synthesis, Characterization, and Antibacterial Evaluation of New 2,3-Dihydroquinazoline-4-One Derivatives and their Laser Efficiency

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Annotation: In this study, a series of novel 2,3-dihydroquinazolin-4-one derivatives [N11–N15] were synthesized through a cyclization reaction between Schiff base intermediates and 2-aminobenzoic acid under mild conditions using tetrahydrofuran as the solvent and triethylamine as the catalyst. The synthesized compounds were structurally confirmed by UV-Vis, FT-IR, and NMR spectroscopic analyses, revealing key functional groups and characteristic transitions associated with quinazoline derivatives. Their antibacterial activity was evaluated against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) using the well diffusion method. The compounds showed variable antimicrobial efficacy, with compound N11 demonstrating the highest inhibition zone, particularly against Staphylococcus aureus (3.2 cm at 0.1 mg/ml), outperforming the standard antibiotic ciprofloxacin in some concentrations. Furthermore, the effect of Nd:YAG laser irradiation on the structural integrity of the compounds was assessed, showing complete decomposition and color change to black charcoal, indicating significant photothermal instability. These results suggest the potential of hydroquinazoline derivatives as promising antibacterial agents, particularly against resistant Gram-positive pathogens.

Keywords: 2,3-dihydroquinazolin-4-

one, bacterial bioactivity, laser.

1. Introduction

The composition of organic compounds with heterocyclic structures relies primarily on non-carbon ring atoms, particularly sulfur, nitrogen, and oxygen, with occasional additions of phosphorus and arsenic. These atoms can be found either inside or outside the ring. This class of compounds encompasses many disciplines, including non-basic sciences such as industrial science, polymer science, and liquid crystal-based optical devices.[1] These disciplines include basic sciences such as chemistry and medicine, as well as non-basic sciences such as art and architecture. Schiff's rules form the basis for the synthesis of complex compounds and have been used to create interesting structures, including hexagonal compounds, for medical use. Several methods have been developed for the synthesis of hydroquinazoline, a chemical known for its anticancer properties. Several types have been proposed: anti-tuberculosis, antibacterial [2], antioxidant, anti-inflammatory[3], and antihelmintic. In addition, anti-cancer [4], anti-viral[5], and anti-malarial variants have been released. More recently, variants have been developed to combat HIV and diabetes[6]. This research was conducted to create and characterize entirely new hydroquinazoline compounds with antibacterial activity against Staphylococcus aureus and Escherichia coli. Given their frequent association with humans, their high presence in soil, and the need to eradicate them, they are under investigation[7,8]. We conducted this research because Staphylococcus aureus is an opportunistic bacterium that causes illness in 30% of people who are unaware of its presence. Many scientists are concerned about the importance of eradicating this bacterium, which is widespread in most hospitals and causes many deaths because it is present in most diseases and impedes wound healing, leading to the emergence of new diseases, especially in patients with diabetes, cancer, eczema, heart disease, and lung disease.

2. Materials and methods

2.1. Material: Aldrich, Fluka, and BDH manufacture all the compounds without refining.

2.2. Synthesis of 2,3-dihydroquinazolin-4-one [N_{15}-N_{11}]

0.0006 mol of the prepared Schiff bases [N_5-N_1] were dissolved in 25 mL of tetrahydrofuran (THF), and 0.00018 mol, 0.25 g of 2-aminobenzoic acid were dissolved in 10 mL of the same solvent. A few drops of triethylamine were added to the mixture, and the mixture was stirred for 20-22 h. The response was confirmed using TLC. The mixture was solidified, filtered, washed with a 10% sodium bicarbonate solution, passed through a filter, finally washed with cold water, and recrystallized with THF[7,8]. The product was then heated to 50 °C, as shown in Table 1.

Table (1) Some physical properties of 2,3-dihydroquinazolin-4-one [N_{15}-N_{11}]

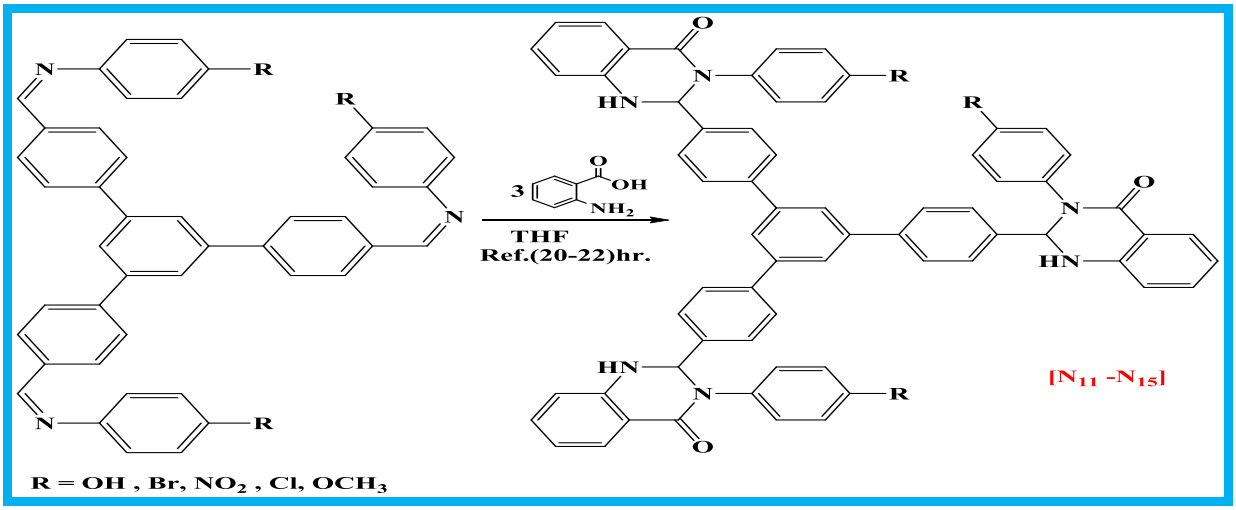
Comp. No.	R	Molecular Formula/ M.Wt g/mol	Color	M.P. (^{0}C)	R.T hour	R_f	Yield (%)
N_{11}	OH	$C_{66}H_{48}N_6O_6$ 1021	Light Brown	>300	21	0.89	71
N_{12}	Br	$C_{66}H_{45}O_3N_6Br_3$ 1209	Light Green	189-191	22	0.78	76
N_{13}	NO_2	$C_{66}H_{45}O_9N_9$ 1108	Off white	132-134	21	0.84	90
N_{14}	Cl	$C_{66}H_{45}O_3Cl_3$ 1076	Light Yellow	148-150	22	0.79	85
N_{15}	OCH_3	$C_{69}H_{54}O_6N_6$ 1123	Light Green	129-131	21	0.90	64

2.3. Evaluation of bacterial bioactivity

Serial two-fold dilutions of the normal saline concentration evaluated the efficacy of the studied compounds. Efficacy is the distance from the highest dilution resulting in the observed growth restriction zone and is expressed in centimeters[9,10]. The procedure for measuring efficacy was called the Wells method. The bacteria used in the test were cultured in a liquid nutrient medium at 37°C for 2 hours. 0.1 ml of the previous culture was transferred to a plate using a diffuser, and the diffuser was then placed on the surface of the plate[11,12]. The plate was then incubated at 37°C for 10 minutes. Half of the compounds were then prepared at serial concentrations of 0.1, 0.01, and 0.001 mg/ml. Wells etching was performed on the plates, and 0.2 ml of each dilution was inserted into each hole. The plates were incubated at 37°C for 24 hours, and the results were recorded to assess whether there was a growth inhibitory effect around each hole[13,14].

2.4. Study of the effect of laser radiation on some prepared compounds

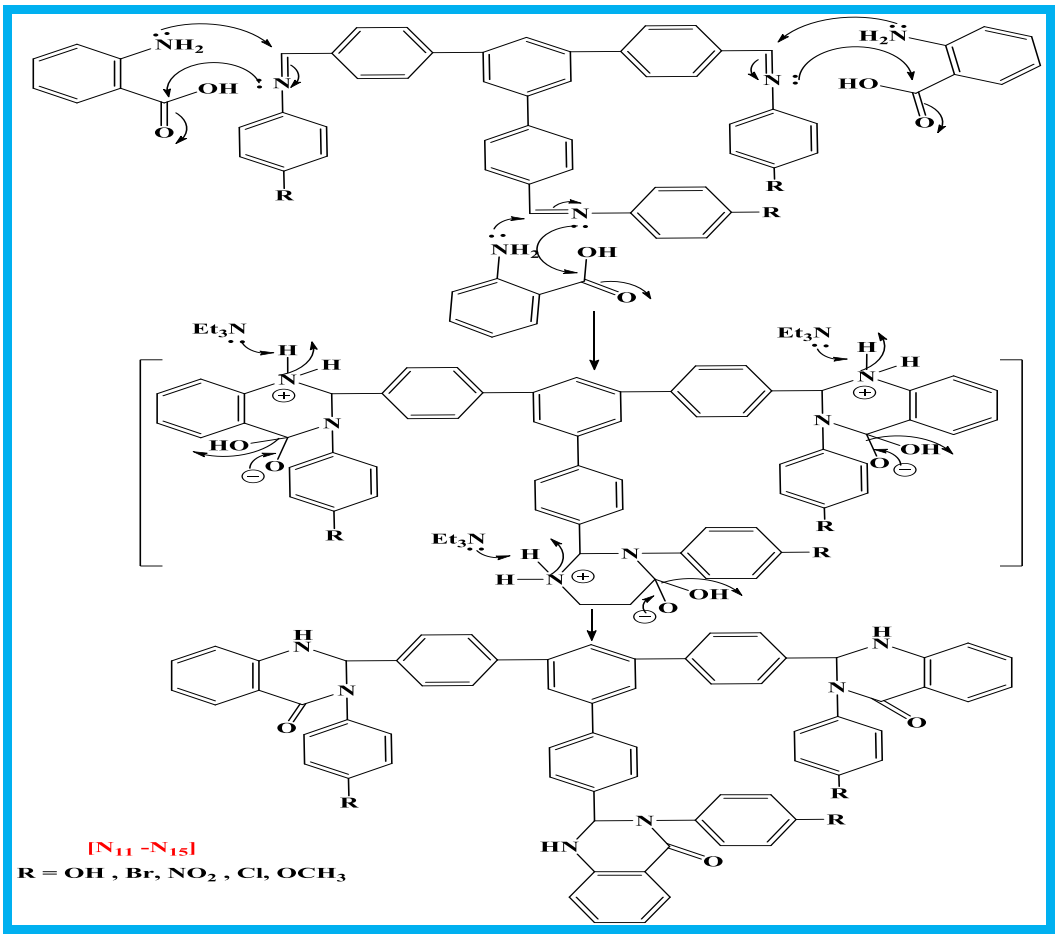
The compounds were exposed to a neodymium nano-laser system (Nd: YAG laser) with a wavelength of 808 nm and a frequency of 5 Hz [N_{11}, N_{12}, N_{13}, N_{14}, N_{15}]. The laser waves were fired for 40 seconds at a distance of 10 cm between the laser source and the samples, and the laser radiation was impacted vertically on the samples using a concave quartz lens with a focal length of 100 mm [15,16].



Scheme (1): Path of the Ready Compounds (N_{11}-N_{15})

3. Results and discussion

2,3-Dihydroquinazoline derivatives [N_{15}-N_{11}] were formed by reacting one equivalent of the prepared Schiff base derivatives [N_5-N_1] with three equivalents of 2-aminobenzoic acid in the presence of THF as a solvent and Et_3N as a catalyst, as can be seen in the following mechanism:



Scheme (2): Mechanism of preparation of 2,3-dihydroquinazoline derivatives [N_{15}-N_{11}].

3.1. Characterization of 2,3-dihydroquinazolin-4-one [N_{15}-N_{11}]

While studying the UV-vis spectrum of [N15-N11] compounds in absolute ethanol as a solvent at a concentration of [10^{-5} - 10^{-4}], short wavelengths ($\lambda_1$max) appeared at (268-245) nm, which are attributed to the ($^*\pi\leftarrow\pi$) transition, while long wavelengths ($\lambda_2$max) appeared at (381-342) nm, which are attributed to the ($^*\pi\leftarrow$n) transition[17].

When studying the infrared spectrum of the prepared [N15–N11] compounds, it was observed that the azomethine (C=N) stretch band that appeared in the prepared Schiff base compounds in the range (1612–1618) cm^{-1} disappeared, indicating the success of the structural transformation reaction and the formation of a 2,3-dihydroquinazoline ring. A medium-intensity band was also observed in the range (3357–3431) cm^{-1}, attributed to the vibration of the N–H bond, confirming the formation of a cyclic amide. In addition, absorption bands appeared in the range (3043–3076) cm^{-1}, attributed to the aromatic C–H stretching, and another in the range (2858–2942) cm^{-1}, attributed to the aliphatic C–H stretching. A strong band was recorded at frequencies (1674–1682) cm^{-1} attributed to the carbonyl amide (C=O) bond stretching, a distinctive spectral feature of this ring. Two clear bands also appeared at the ranges (1452–1481) cm^{1} and (1519–1583) cm^{1-1} attributed to the vibrations of the C=C bond in the aromatic ring, in addition to bands at (1208–1216) cm^{1} attributed to the C–N bond stretching. These results are consistent with the values reported in the chemical literature [18,19]. As in Table 2 and Figure 1,2

Table (2): FT-IR absorption results for 2,3-dihydroquinazoline derivatives (N_{11}-N_{15})

Comp. No.	λ max$_1$ λ max$_2$ EtOH	R	IR (KBr) cm^{-1}					
			νN-H νC-H Arom.	νC-H Aliph.	νC=O	νC=C Arom.	νC-N	Others
N_{11}	261 342	OH	3357 3064	2925	1682	1573 1452	1216	ν (OH) 3476
N_{12}	251 352	Br	3396 3048	2942	1675	1581 1475	1208	ν (C-Br) 576
N_{13}	247 353	NO_2	3431 3043	2937	1674	1583 1481	1211	ν(NO_2)*asy*. (1523) *sym*. (1340)
N_{14}	268 381	Cl	3416 3057	2936	1679	1574 1469	1215	ν (C-Cl) 727
N_{15}	245 363	OCH_3	3363 3076	2931 2858	1680	1519 1462	1211	ν (C-O-C)*asy*. (1346) *sym*. (1280)

When studying the 1H-NMR spectrum of the compound [N_{13}] in the solvent (DMSO-d6), signals were observed in the range (6.91-8.18) ppm, which were attributed to the protons of the aromatic rings, as well as the chemical shift (6.33) ppm, which was attributed to the (NH) group in the quinazoline ring, and the appearance of one signal at the chemical shift (5.78) ppm, which was attributed to the (CH) groups in the quinazoline ring, as well as the appearance of a signal at position (2.52) ppm, which was attributed to the protons of the solvent (DMSO-d^6). As in Figure 3

When studying the ^{13}C-NMR spectrum of [N_{13}] compound in the solvent (DMSO-d6), a signal was observed at the chemical shift (168.10) ppm associated with the carbonyl group carbon (C=O), in addition, multiple signals were observed at the chemical shifts (112.82-156.20) ppm associated with the carbon atoms in the aromatic ring, a signal was observed at the chemical shift (90.04) ppm associated with the carbon of the (CH) group in the quinazoline ring, and a signal was observed at the chemical shift (39.12-40.78) ppm associated with the carbon of the solvent (DMSO-d^6).As in Figure 4

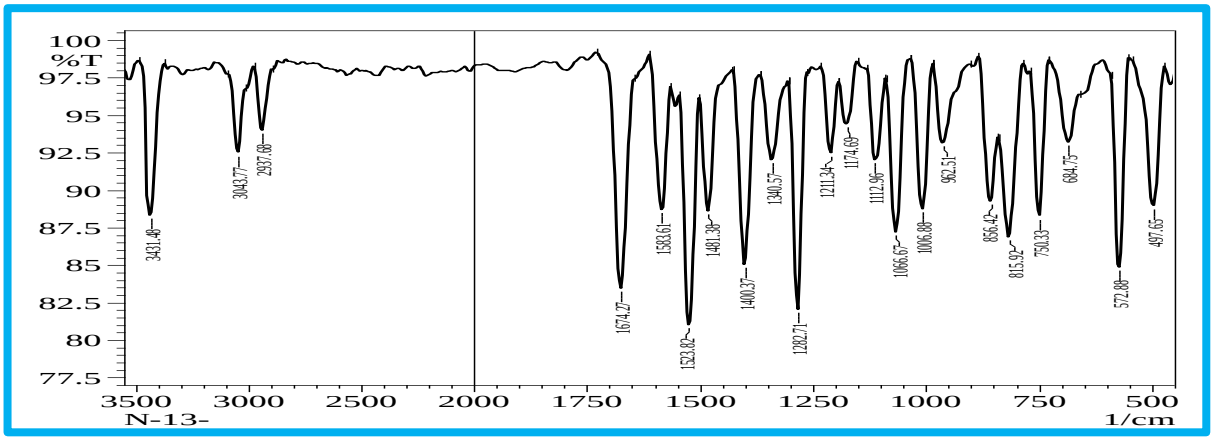


Figure (1): The compound's FT-IR spectra (N_{13}).

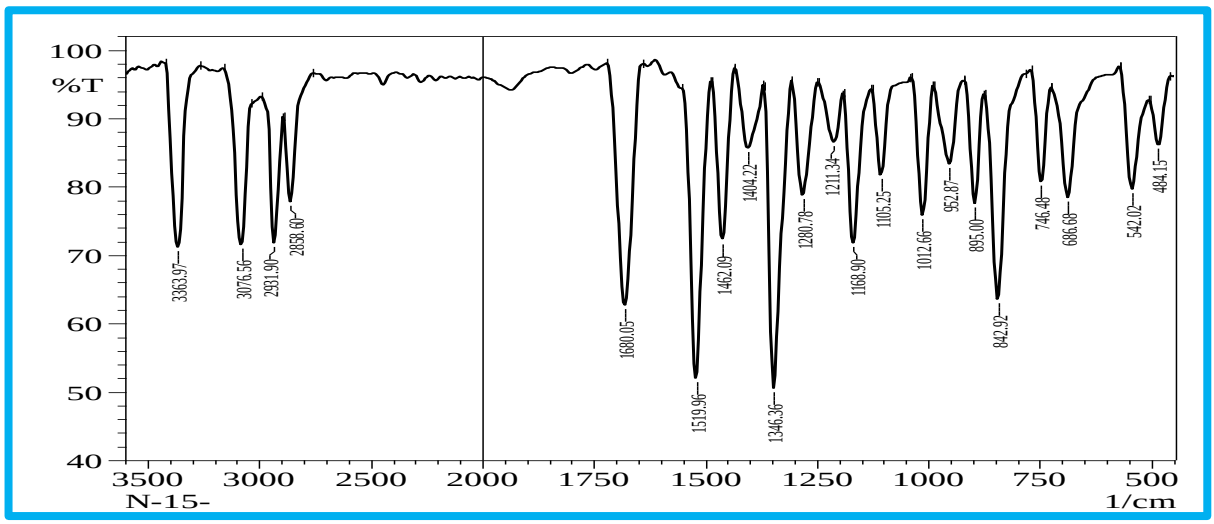


Figure (2): The compound's FT-IR spectra (N_{15}).

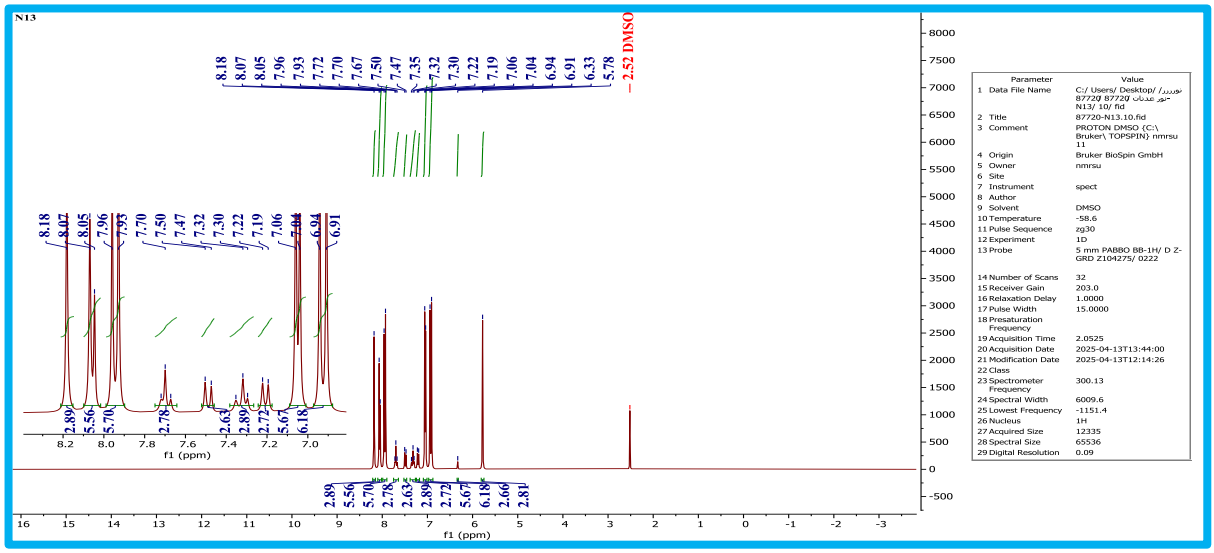


Figure (3): 1-H NMR spectra of the substance (N_{13}).

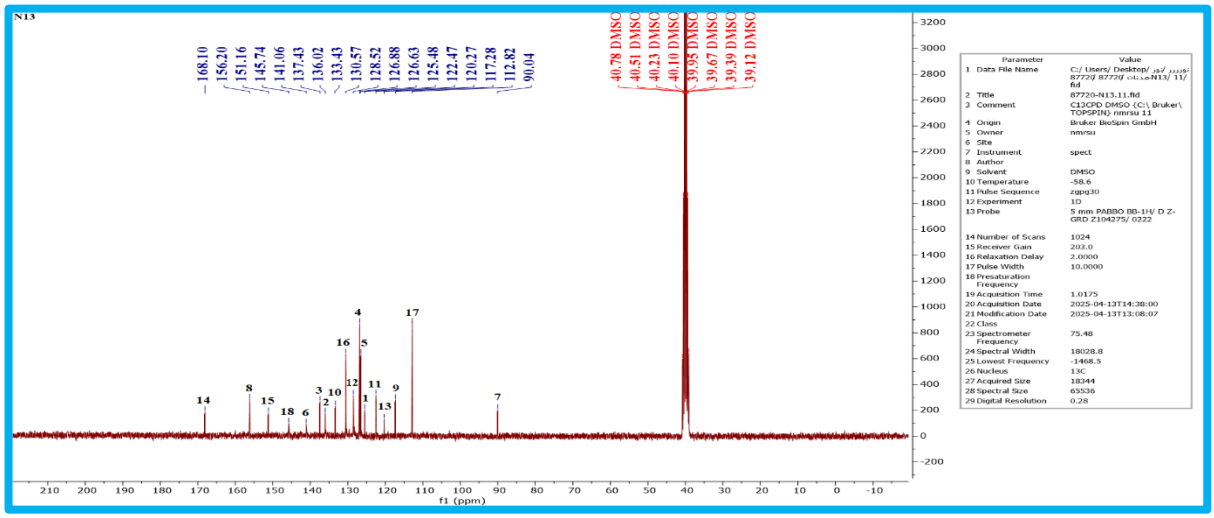


Figure (4): ^{13}C- NMR spectra of the substance (N_{13}).

3.2. Bacterial susceptibility to prepared compounds

The inhibition test results showed that the prepared compounds possessed varying biological activity against Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-

positive)[20,21]. Most compounds were observed to be more effective against Gram-negative bacteria, which is consistent with the nature of the E. coli cell wall, which consists of a thin layer of peptidoglycan surrounded by an outer membrane rich in lipids, which may facilitate the permeation of some chemical compounds with suitable properties[22,23]. Compound [N_{11}] emerged as the best compound, recording an inhibition diameter of 3.2 cm at the highest concentration. It is worth noting that the cell wall of Gram-positive bacteria is characterized by a thick and dense peptidoglycan layer, which may limit the effectiveness of some compounds and require specific chemical properties (such as positive charge or hydrophobic groups) to increase permeability[24,25]. As in Table 3 and Figure 5,6

Table (3): Antibacterial activity of the synthesized compounds (inhibition zone in cm).

Comp No.	E.coli mg/ml			Staph. aureus mg/ml		
	0.1	**0.01**	**0.001**	**0.1**	**0.01**	**0.001**
N_{11}	2.1	0.3	0.4	3.2	1.8	1.2
N_{12}	1.5	0.4	2.3	2.0	1.2	1.5
N_{13}	1.8	1.1	1.0	1.7	1.2	0.7
N_{14}	1.6	1.2	0.5	0.5	0.5	0.5
N_{15}	1.2	1.0	0	1.3	1.0	0.5
Ciprofloxacin	2.0	1.5	1.3	1.5	1.5	1.2

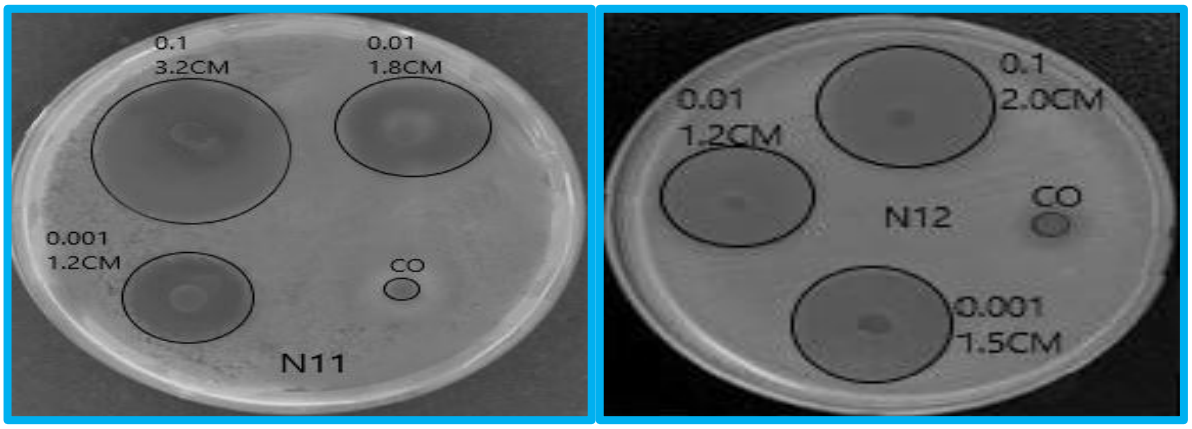


Figure (5): Inhibitory activity of the two compounds (N_{11},N_{12}) against *Staph. ureus*

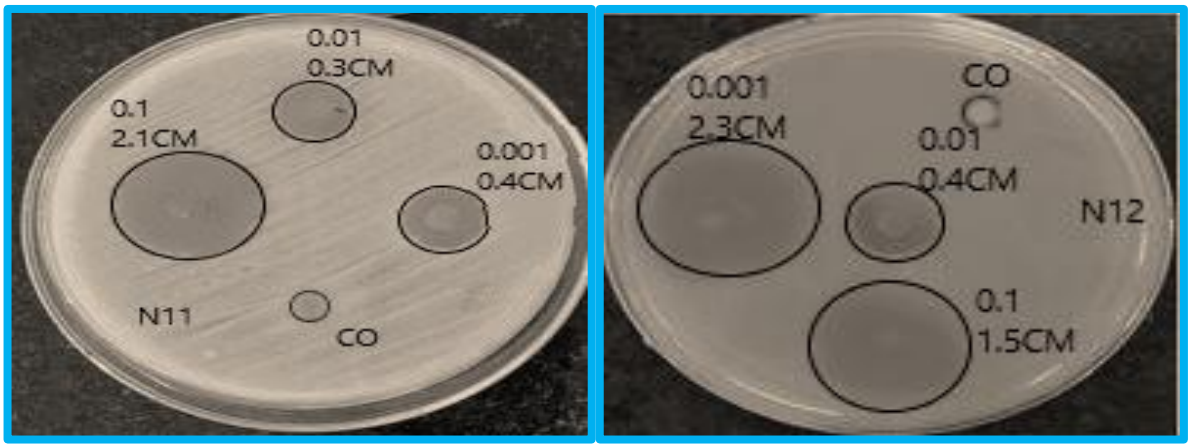


Figure (6): Inhibitory activity of the two compounds (N_{11},N_{12}) against *E.Coli*

3.3. Results of measuring the laser activity of some prepared compounds

In this study, the laser activity of several prepared compounds [N_{11}, N_{12}, N_{13}, N_{14}, N_{15}] was evaluated by irradiating them with a nanosecond neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser at a wavelength of 808 nm and a frequency of 5 Hz. 40-second laser pulses were

delivered to each sample, with a distance of 10 cm between the laser source and the sample. After irradiation, the changes in the physical properties of the compounds, including color and melting point, as well as the changes caused by the laser pulses, were evaluated (15). The results showed that the compounds underwent significant changes after irradiation, manifested by a black color change and loss of their original structure, the latter of which was attributed to changes in the structural properties of these compounds. As in Table 4

Table 4: Results of measuring the laser activity of some prepared compounds

Comp. No.	Before Irradiation		After Irradiation	
	M.P. ^{0}C	Color	M.P. ^{0}C	Color
N_{21}	>300	Light Brown	-	Charcoal
N_{22}	189-191	Light Green	-	Charcoal
N_{23}	132-134	Off white	-	Charcoal
N_{24}	148-150	Light Yellow	-	Charcoal
N_{25}	129-131	Light Green	-	Charcoal

4. Conclusions

This research successfully synthesized and characterized a new series of hydroquinazoline-based compounds with significant antibacterial activity. Spectroscopic analyses confirmed the structural integrity of the synthesized derivatives. Among the tested compounds, N_{11} exhibited superior antibacterial effectiveness, especially against *Staphylococcus aureus*, suggesting its potential as a lead compound for further drug development. The differential activity between Gram-negative and Gram-positive strains was attributed to the structural differences in their cell walls. Moreover, laser irradiation studies revealed that these compounds are photothermally sensitive, undergoing complete degradation upon exposure, which limits their stability under light but could open pathways for potential photoresponsive therapeutic applications. Future studies will focus on enhancing the stability and selectivity of these compounds for broader pharmacological uses.

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